Barriers to Drug Delivery in Solid Tumors

Many tumors resist full penetration by anticancer agents. Such resistance may help explain why drugs that eradicate tumor cells in laboratory dishes often fail to eliminate malignancies in the body

by Rakesh K. Jain

An agent that destroys cancer cells in a culture dish should, in theory, be able to kill such cells in the body. Certain drugs that display potent anticancer activity in the laboratory have indeed saved the lives of many patients, particularly those suffering from various pediatric cancers or malignancies of the blood. Sadly, however, [redacted] has not [redacted] the most [redacted] and [redacted]

No single process is likely to explain the disappointing results. Nevertheless, recent research indicates that a much overlooked property of tumors [redacted] ly, resistance to penetration by drugs—[redacted] ing therapy. After cancer-fighting drugs are [redacted] they travel via the bloodstream to their targets. To eradicate tumors, the agents must then disperse throughout the growths in concentrations high enough to eliminate every deadly cell. Yet studies my colleagues and I have conducted during the past 20 years show that solid cancers frequently impose formidable barriers to such dispersion. Investigation of those barriers is now generating [redacted] for overcoming them.

Success in combating the obstacles should [redacted] many different approaches to therapy, all of which have as a common denominator that their effectiveness depends on optimal accumulation of therapeutic agents in tumors. Whenever possible, physicians treat solid cancers by surgical removal or by irradiation. If, however, parts of an original (primary) mass cannot be excised or if the tumor is thought to have metastasized, doctors may rely on systemic drug therapy to eliminate any remaining cancerous tissue.

Systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (including unfortunately, healthy ones). More recently, genetic engineering and other technologies have provided a second class of drugs—proteins and other biological products. This class encompasses several molecules of the immune system, such as tumor necrosis factor, interleukins, interferons and monoclonal antibodies. It also includes white blood cells known as lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocytes, as well as various agents designed to carry out gene therapy.

Radiation therapy may similarly incorporate delivery of blood-borne drugs. Radiation works in part by converting oxygen molecules into highly destructive forms called free radicals. Yet tumors are frequently oxygen deficient. In an attempt to increase the vulnerability of malignancies to the treatment, investigators are testing the value of administering sensitizing agents that mimic oxygen or somehow elevate oxygen levels in a tumor. Malignancies can also be killed by heating, and so hyperthermic therapies sometimes involve drugs that increase a tumor's response to heat. In photodynamic therapy, a compound that is relatively harmless until it is exposed to laser light is injected and given time to collect in a tumor. Then light is focused on the mass.

I was a graduate student in chemical engineering at the University of Delaware when I first became intrigued by the [redacted] 1974 James Wei, my Ph.D. adviser, arranged for me to assist Pietro M. Gullino of the National Cancer Institute in measuring the uptake of drugs by malignancies in animals. As I learned more and more about cancer, it became obvious to me that the failure of blood-borne agents to distribute [redacted] determine [redacted] to wonder whether solid tumors possessed features that [redacted] I also began to think that my engineering background, including my understanding of fluid and molecular transport, could aid in exploring that possibility.

The likelihood that tumors could impede drug distribution was suggested partly by their structure. Contrary to popular perception, malignant growths are not merely clusters of proliferating

IDEALIZED SOLID TUMOR has been partly cut away to reveal some of its blood vessels. Before a blood-borne drug can begin to attack malignant cells in a tumor, it must accomplish three critical tasks (*detail*). It has t make its way into a microscopic blood vessel lying near malignant cells in the tumor (*1*), exit from the v ssel into the surrounding matrix (the interstitium) (*2*) and, finally, migrate through the matrix to the cells (*3*). Unfortunately, tumors often develop in ways that hinder each of these steps.

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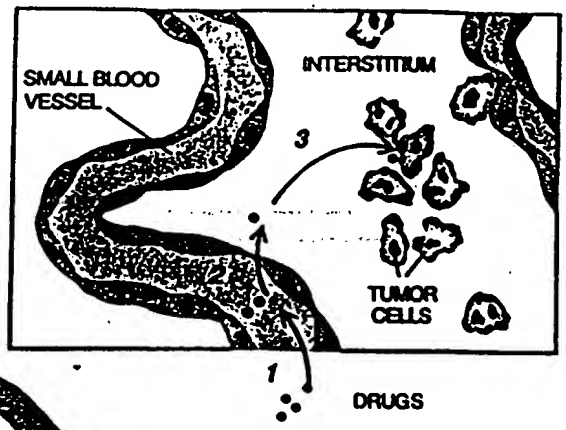
cells. Cancer cells often occupy less than half the volume of a tumor. One to 10 percent of the volume is contributed by blood vessels weaving through the tumor mass. The remaining space is filled primarily by an abundant collagen-rich matrix—the interstitium—that surrounds cancer cells and can separate them from the vasculature. (Healthy tissue contains an extracellular matrix as well, but the interstitium in tumors is usually more extensive.)

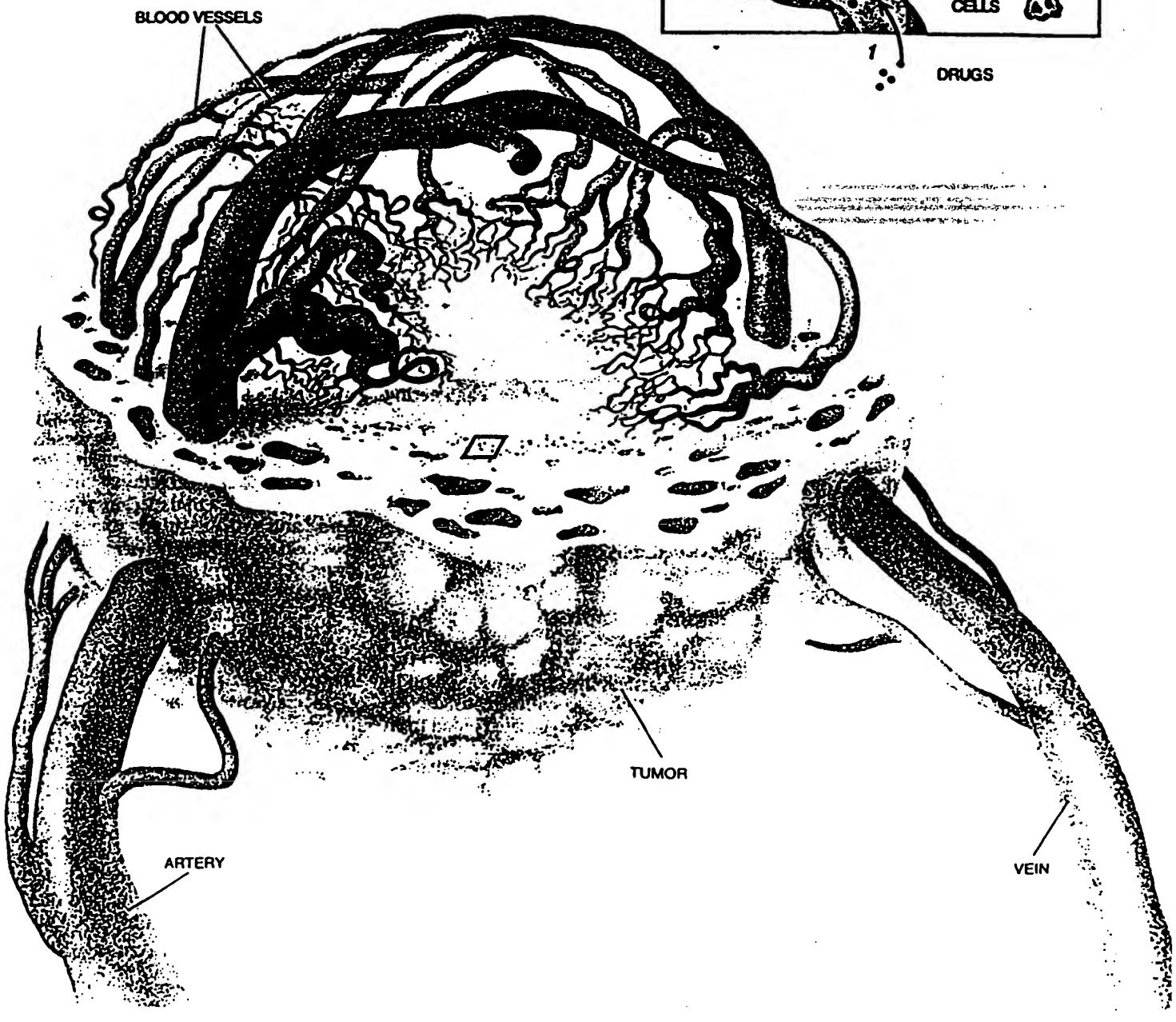
To reach cancer cells in a tumor, then, a therapeutic agent must make its way into the blood vessels of the tumor and across the vessel wall into the interstitium. Finally, it must travel, often great distances, through that matrix to the cells. Accomplishing any of those steps, I reasoned, could be problematic.

I was unable to pursue this idea when I obtained my first faculty position, but my opportunity came in 1978, the year I moved to Carnegie Mellon University. My colleagues and I—a multidisciplinary group—have been studying barriers to drug penetration ever since, most recently at Harvard University and at Massachusetts General Hospital, which I joined in 1991.

We apply several methods in our work. For example, at Carnegie Mellon, we immediately adopted a method introduced by Gullino in 1961. In this approach we grow tumors in rodents so that each cancerous mass is connected to the circulatory system by a single artery and a single vein. That arrangement enables us to measure how much drug flows into and out of a tumor. From such information, the amount of drug that is retained can be calculated. We also developed a related procedure that permits the study of colon cancers arising spontaneously in humans. When surgeons remove tumors from patients, they can occasionally provide us with individual nodules fed by one artery and drained by one vein. We then maintain the circulation artificially.

Although these approaches yield valuable information, the inner workings of the tumors remain something of a black box. To obtain detailed insight



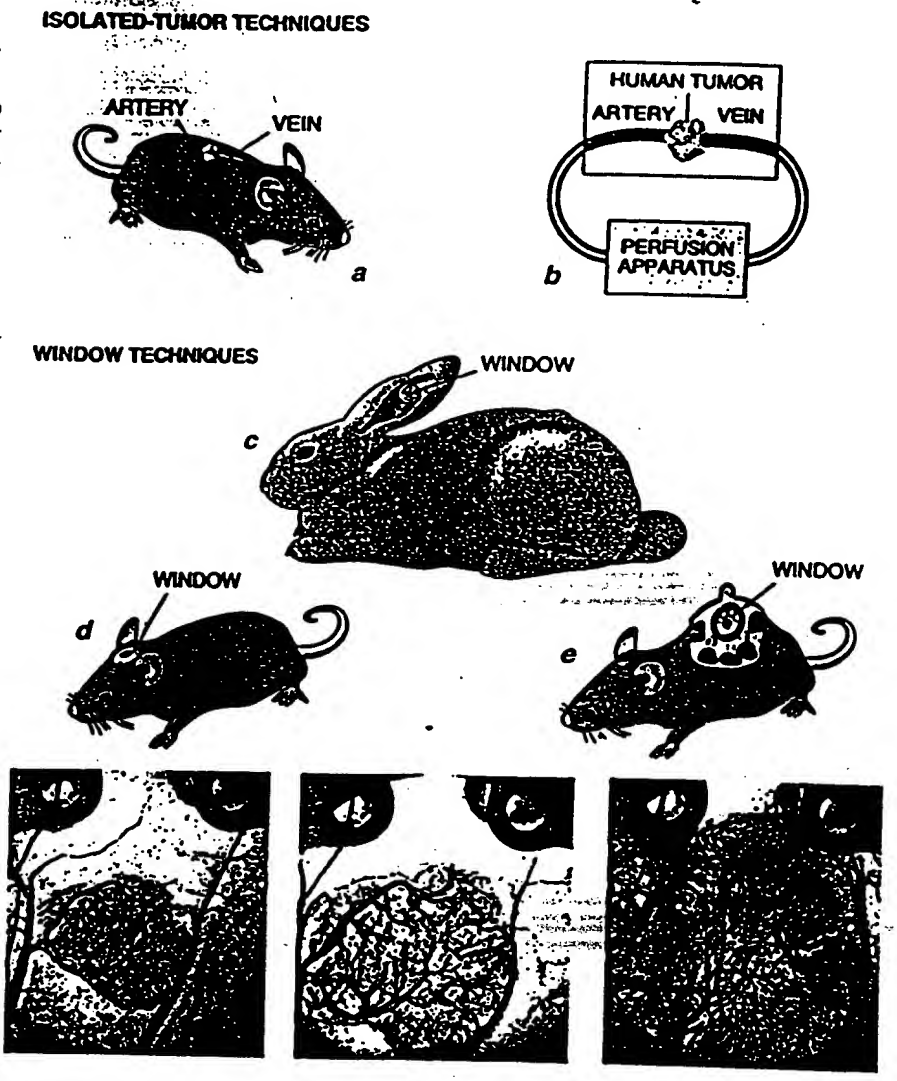


How Drug Delivery Is Studied Experimentally

The author's group applies two main experimental strategies for determining the fate f drugs in tumors. In "isolated tumor" techniques the workers implant into a rodent a tumor that is fed by a single artery and drained by a single vein (*a*), or they occasionally obtain such a tumor from a human patient and keep blood flowing artificially (*b*). Then they measure the amount of drug entering and leaving the tumor and calculate the amount absorbed.

In "window" techniques the investigators grow a tumor in the ear of a rabbit (*c*) or on the brain (*d*) or dorsal skin (*e*) of a rodent and put a glass cover slip on the tumor. By focusing a microscope on the visible tissue, they can directly observe such phenomena as the development of new blood vessels and the spread of a drug through a tumor.

The photographs track changes that occurred between the fifth day and 20th day (*left to right*) after cancer cells were implanted in the dorsal skin of a rodent. By day 20, the periphery of the resulting tumor had gained a tangle of blood vessels, but the center had lost much of its blood supply (*white area*). The tumor thus lost vessels needed for bringing blood-borne drugs directly to the central region.



into the flow of blood and the distribution of drugs and other substances in a tumor, we apply modified versions of "window" techniques that were introduced for use in rabbits by J. Calvin Sandison of the University of Pennsylvania in the 1920s and for use in mice by Glenn H. Algire of the National Cancer Institute in the 1940s.

We implant tumor cells in the ear of a rabbit or on the brain or back skin of a rodent. Then we cover them with a transparent glass cover slip or sandwich them between two cover slips. As the resulting tumor grows against the glass, we can observe it under a microscope. By attaching fluorescent labels to injected agents, we can even trace the passage of various substances through the tumor. Since 1991 ur access to immunodeficient mice has enabled us to view human tumors, not merely those of animal origin. (The lack of an immune system prevents the mice from rejecting the human grafts.) Mathematical modeling, a classic engineering strategy, aids our investigations as well. It allows us to combine theory with experiment, to formulate and test predictions, and to minimize the number of animals in our experiments.

Early on, our work and that of others revealed that the vascular system of tumors can be highly disorganized, both in its structure and its operation. This disorganization, in turn, can form one important barrier to drug delivery. In normal organs, blood vessels are arrayed predictably and provide blood to all areas of the constituent tissue. Arteries delivering oxygenated blood from the heart divide into smaller arterioles and then into microscopic capillaries. From the capillaries, fluid, nutrients and oxygen pass into the surrounding matrix and cells. The capillaries feed into venules, which take up wastes and excess fluid from the tissue and deliver them to veins for removal.

Although tumors initially obtain blood from the existing vasculature in the region, they eventually produce new small blood vessels, which branch excessively, twist into tortuous shapes and grow in unpredictable directions that can change from day to day. Consequently, some areas of the tumor may be well vascularized, whereas others have little or no blood supply.

These findings thus indicated that one of the first problems a blood-borne drug encounters en route to cancer cells is an uneven distribution of blood vessels. Indeed, through our transparent windows we can see that regions lacking blood vessels receive no drug directly from the circulation. (Tumor cells in those blood-starved areas may seem, on superficial inspection, to be dead, but they frequently revive if nourishment returns.)

What is more, the aberrant branching and twisting of the vasculature often contribute to an observable slowing of

blood flow—a phenomenon that is exacerbated by the unusual viscosity of the blood in tumors. The slowed flow hinders delivery of drugs to poorly perfused regions of the tumor. It also participates in causing other drug-delivery problems, as will be seen.

The nonuniform blood supply is by no means the only obstacle to the spread of a drug in a tumor. A second impediment takes the form of abnormally high pressure in the interstitial matrix (as measured by the force the matrix exerts on a probe inserted into it). The pressure can retard the passage of large molecules across vessel walls into the interstitial matrix. It can thus contribute to the low concentration of drug molecules frequently seen (by fluorescence microscopy or other imaging techniques) in the interstitial matrix of animal and human tumors growing in mice.

We began to suspect that interstitial pressure might pose problems for drug delivery when we took a close look at the forces that control the movement of molecules from the blood into the matrix. Such passage occurs across or between endothelial cells, which line vessel walls in a single layer. We knew that molecules leave blood vessels (extravasate) primarily by two mechanisms: diffusion and convection. (Cells, which I shall discuss separately, use a third option as well.) Diffusion is the movement of molecules from an area of high concentration to an area of lower concentration. Convection is the transport of molecules by a stream of flowing fluid. Unlike diffusion, which is unaffected by pressure gradients, convection is governed by them: fluid flows from areas of high pressure to areas of low pressure, carrying molecules with it.

The difference between the two processes can be illustrated by a simple example. When a blob of ink is dropped into a glass of still water, the ink molecules spread gradually outward—by diffusion—until a uniform concentration is achieved. If, however, water in a glass is stirred after a drop of ink is added, the swirling water rapidly distributes the ink wherever the fluid travels.

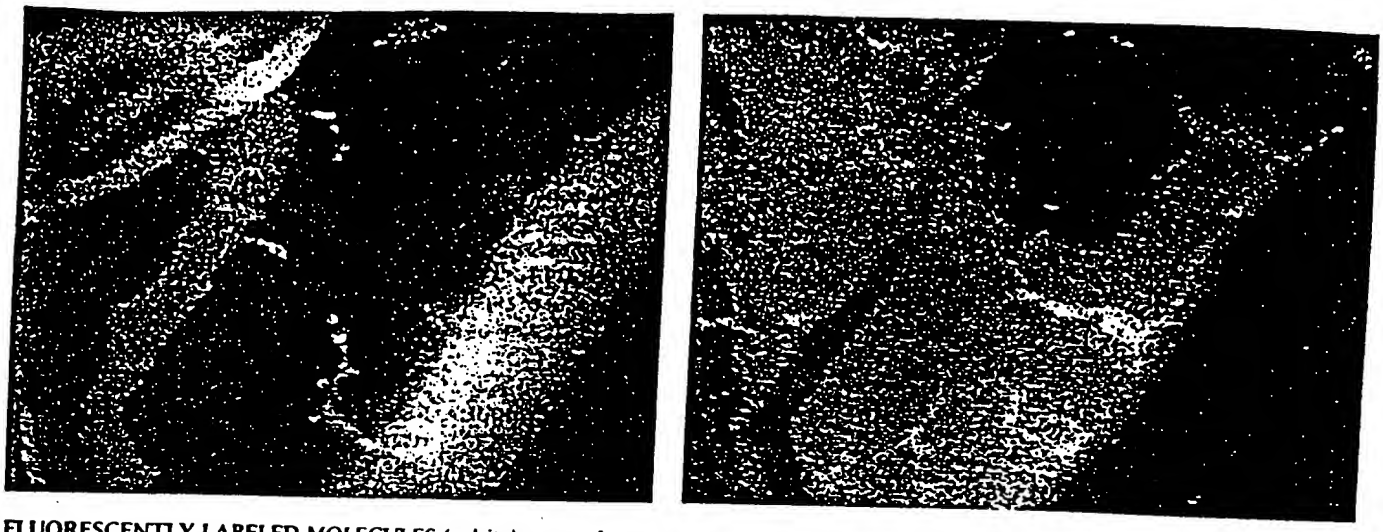
We knew, too, that small molecules—such as oxygen and conventional chemotherapeutic drugs (which have a molecular weight lower than 2,000 daltons)—leave blood vessels and migrate through normal tissue mainly by diffusion. But large molecules—including genetically engineered drugs (which have a molecular weight greater than 5,000 daltons)—move mainly by convection.

In healthy tissue, convective movement of large molecules from the blood into the interstitium occurs because the pressure in the capillary network is higher than the pressure in the interstitial tissue (which is approximately zero). But what happens in tumors? In 1987 I proposed that if the interstitial pressure in solid tumors was abnormally high, the convective passage of large drug molecules into the interstitium would be impeded. Some big molecules would still enter the matrix by diffusion but not rapidly, because the rate of passage by diffusion becomes slower as size increases.

In order to begin testing this hypothesis, my colleagues and I set out to determine whether interstitial pressures in human tumors are indeed elevated. Two early discoveries lent support to that possibility. First, a review of the scientific literature revealed that in 1950 J. S. Young and his co-workers at the University of Aberdeen had measured interstitial pressure at the center of rabbit tumors that were transplanted into other rabbits; the pressure in the tumors was higher than that in normal tissue. Other groups had subsequently published similar findings. The relevance to spontaneous human tumors was unclear, though, and so these discoveries were largely ignored.

Second, when one of my graduate students and I developed a mathematical model of pressure distribution in solid tumors in 1988, the model suggested that interstitial pressure would be high. In fact, it produced the unexpected prediction that the pressure would be equally high throughout the bulk of a

CAST OF BLOOD VESSELS in a half-pound human tumor is shown in two views. It was made by injecting a blue polymer into the vessels of a surgically excised colon cancer and then eliminating all tissue. The region resembling a crystal in the full cast (*left part of top image*) was formed by a chaotic cluster of microscopic vessels; the hole at the center of the region arose because the area lacked a blood supply. The close-up view (*bottom*) highlights one of many structural abnormalities of tumors: a number of the vessels are tortuous and twist into corkscrewlike coils that can contribute to a marked slowing of blood flow.



FLUORESCENTLY LABELED MOLECULES (*white*) were photographed soon after they entered small blood vessels in the outer rim of a tumor (*left*) and, later, after they began seeping into the interstitial matrix surrounding the vessels (*right*). The molecules were able to cross some vessel walls into the matrix but not others, such as the right wall in the rightmost vessel. They also made their way through parts of the matrix but not through others, such as the black region at the top. The differences result to a great extent from variability in the porosity of both the vessels and the matrix in the periphery.

tumor. Then the pressure would drop steeply to near zero in the periphery, where it would approach the low pressures in the surrounding normal tissue.

The finding of a uniformly elevated pressure profile startled us because every other parameter that had been measured in tumors (or has since been measured) was nonuniform. Not only is the distribution of blood vessels uneven and changeable, but the rate of blood flow can also change with time, even in a single vessel. Moreover, some vessels are extremely porous, or leaky, whereas others are not. And a single vessel can be abn rmally leaky in one region but relatively nonporous in another.

No experimental data in the scientific literature could confirm or refute the model's predictions, and so a postdoctoral fell w in my group undertook to measure interstitial pressures throughout animal tumors. As predicted, he found that the pressure in large solid tumors (those greater than about half a centimeter in diameter) was uniformly high everywhere except in the outer rim. Other laboratories have now confirmed these results in animals. Since 1990 we have collaborated with physicians at the University of Pittsburgh, at the University of Munich and at Massachusetts General Hospital to measure pressures in solid tumors of patients undergoing treatment. The pressures are as high as those in animals, sometimes higher.

Part of the 1987 hypothesis has thus been borne out: interstitial pressure in large tumors is abnormally high. But is the elevation sufficient to cause serious impairment of the convective flow of large drug molecules? That is, is the pressure in interstitial tissue equal to or higher than the pressure in the microvascular network? Our mathematical model suggested they would be about equal. Simultaneous measurements of microvascular and interstitial pressures in animal tumors have recently validated this prediction. The measurements also indicate that the pressure in tumor blood vessels is higher than it is in normal capillaries. We think this elevation stems mainly from the direct and indirect compression of the vessels by proliferating cells. The unusual architecture of the vasculature and the high viscosity of blood in tumors apparently contribute as well.

Together the experimental and theoretical findings fit well into the following scenario for the development of pressure-related barriers to drug accumulation in the interstitium. A tumor initially grows in the midst of normal tissue and makes use of the existing vasculature. At this stage, it displays low interstitial and vascular pressure and relies on the existing lymphatic system to drain excess fluid from the interstitial matrix. As the tumor grows, it produces new, often leaky blood vessels but is unable to form its own lymphatic system. Meanwhile the abnormal geometry of blood vessels slows the rate of blood flow. This slowing, combined with compression by tumor cells and other factors, elevates the pressure in the vessels. Fluid seeps copiously out of them into the matrix and, in the absence of a functional lymphatic system, is not removed efficiently.

As the fluid builds in the interstitium, so does the pressure. Eventually the pressure in the vessels and the matrix equalizes. At that point, small molecules flowing in the blood continue to escape readily by diffusion (albeit only in areas that still have a blood supply). But larger molecules often remained confined in blood vessels, except in the periphery, where interstitial pressure is close to normal. Some large molecules do cross into the interstitium by diffusion, but they do so slowly. Hence, the body can eliminate most of them from the circulation before they can accumulate to optimal concentration in tumors.

The challenges faced by therapeutic agents persist even after they find their way into the interstitium. To be fully effective, they must spread throughout the matrix to cells not directly fed by blood vessels. Small molecules make the trip fairly easily (by diffusion) if they are not degraded, reabsorbed by microvessels or stopped by other processes. But large, convection-dependent molecules have a much harder time; the uniform pressure in most of a tumor's interior keeps convection from operating there.

Ironically, convection does function in the periphery—regrettably, in the wrong direction. Recall that pressure plummets at the tumor margin, where it approaches that of the surrounding normal tissue. In consequence, fluid flows from the outermost boundary of the high-pressure region into the periphery and away from the cancer. Gullino measured the magnitude of this movement in 1974. He found that approximately 10 percent of the blood fluid leaving a solid tumor oozes out from its periphery rather than draining via a vein. We and others have since confirmed his finding. The liquid escap-

ing from the tumor surface carries drug molecules out and away from the tumor in the process.

For molecules that remain in the interstitium, the often slow process of diffusion is the only available means of dispersion to poorly perfused areas. In mathematical terms, the time required to move some distance by diffusion is proportional to the square of the distance. That is, if it takes a molecule one minute to travel one micron, the molecule will require four minutes (2^2) to move two microns and 16 minutes (4^2) to move four microns. In contrast, the time required to move by convection, if it were operating, would be directly proportional to the distance alone. In other words, a molecule that spent one minute traveling across one micron of tissue by convection would require only two minutes to travel two microns and four minutes to travel four microns.

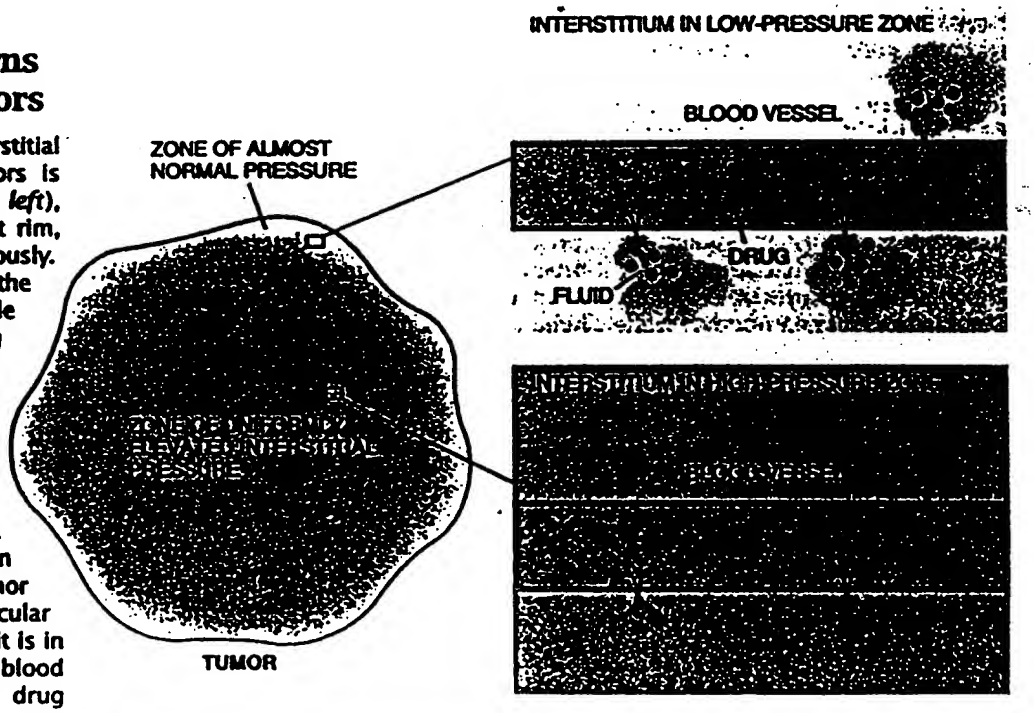
How long might it take for macromolecules at the periphery of a tumor to spread to the center by diffusion? To gain a sense of the answer, we injected molecules having different sizes, shapes and charge distributions into animals and measured the time it took for them to pass through the tissue visible in our transparent windows. We then fed this information into a mathematical model that allowed us to calculate the time it would take for the molecules to reach uniform concentrations in tumors of different sizes and physiological characteristics. We found, for instance, that a continuously supplied monoclonal antibody having a molecular weight of 150,000 daltons could take several months to reach a uniform concentration in a tumor that measured one centimeter in radius and had no blood supply in its center.

Such slow spread could easily hinder the ability of macromolecules, including the new generation of genetically engineered drugs, to eradicate tumors. Agents delivered to the bloodstream do not survive there indefinitely. Repeated doses would therefore have to be delivered to maintain elevated concentrations in the blood for as long as would be needed to achieve complete penetration of a tumor. Ongoing delivery would not only be expensive, it could also be harmful to some normal tissues that took up the drugs. (For any drug to be acceptable as a therapy, it must work without causing serious irreversible damage to healthy tissue.) Repeated dosing could also lead the immune system to manufacture antibodies and other agents that would degrade the drug before it could achieve its maximal effect.

Other impediments to passage in the interstitium are also under investigation by us and by others. These studies indicate that many genetically engineered drugs are sticky; this property

Pressure Patterns in Human Tumors

Pressure in the interstitial tissue of solid tumors is uniformly elevated (*top left*), except in the outermost rim, where it drops precipitously. The elevated pressure in the inner zone can impede movement of large drug molecules into the matrix from the bloodstream—for a simple reason. Large molecules travel mainly by convection, flowing in fluid from a high- to a low-pressure region. In the outer zone of a tumor (*top detail*), the vascular pressure is higher than it is in the interstitium, and so blood fluid (*gray*) laden with drug molecules (*blue*) seeps (*arrows*) into the interstitium. In the inner zone (*bottom detail*), the interstitial pressure is about equal to that in the blood vessels; hence, convection virtually ceases. High interior pressure, which was predicted by a mathematical model, has now been found in humans (*table*) as well as in animals. The pressure readings listed are measured in millimeters of mercury.



INTERSTITIAL PRESSURE IN HUMAN TUMORS

TYPE OF TISSUE	NUMBER OF PATIENTS	MEAN PRESSURE
NORMAL BREAST	10	0.1
NORMAL SKIN	5	0.4
RENAL CELL CARCINOMAS	1	38.0
CERVICAL CARCINOMAS	26	22.8
COLORECTAL LIVER METASTASES	8	21.0
HEAD AND NECK CARCINOMAS	27	19.0
BREAST CARCINOMAS	8	15.0
METASTATIC MELANOMAS	12	14.3
LUNG CARCINOMAS	26	10.0

slows the rate of diffusion, just as sticky shoe soles would handicap someone running a race. Moreover, enzymes in the interstitial compartment might degrade some drugs before they have the opportunity to act on target cells. Tumors also display metabolic disorders that can reduce the effectiveness of some drugs and radiation. For instance, the relative lack of oxygen in tumors may lead cancer cells to secrete high levels of lactic acid. A number of drugs will break down or fail to work in an acidic environment.

Oddly enough, the very factors that act as impediments to penetration can occasionally be beneficial. For example, stickiness can help retain a drug in a tumor. Some drugs work better in an acidic or hypoxic environment. Further, if a compound can overcome the multifarious roadblocks and eventually accumulate in a poorly vascularized area, the lack of a blood supply becomes a bonus. In what we refer to as the reservoir phenomenon, the accumulated drug, which has few avenues of escape, can serve as a reservoir that releases the drug gradually into neighboring regions of a tumor.

Certain barriers that confront drug molecules also hinder the delivery of white blood cells administered as anticancer weapons. The heterogeneous blood supply of tumors is clearly a major barrier, just as it is for molecules. We are still trying to determine the extent to which cancers resist extravasation and interstitial migration by white cells. The cells' ability to leave blood vessels may depend less on pressure gradients than on their ability to attach to endothelial cells in vessel walls and to deform themselves in ways that increase their contact with the wall. These behaviors help the cells to squeeze between endothelial cells and thus propel themselves out of the vascular system.

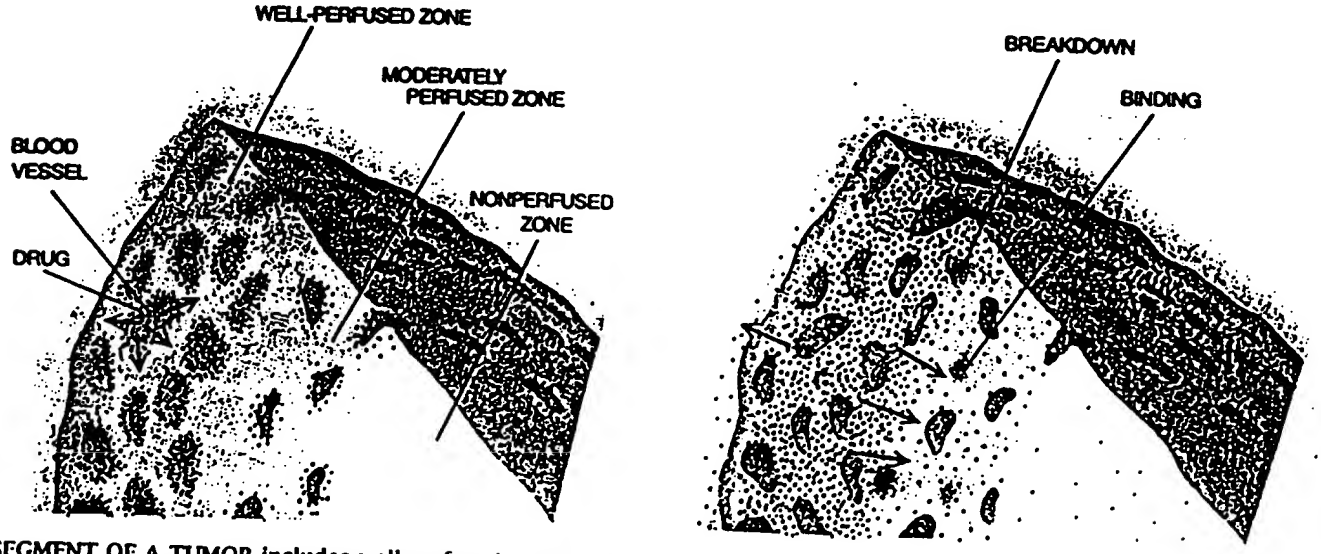
Once cells are in the interstitial matrix, they migrate by attaching to the matrix and crawling through it. The efficiency of this movement is again influenced by the cells' adhesive properties and deformability as well as by various characteristics of the tumor tissue. For instance, certain molecules in the tumor milieu can facilitate or hamper cell motility; others control the direction in which the cells migrate. More study of these processes is needed.

I should note that when therapeutic cells or molecules eventually reach cancer cells, their problems do not end. They may encounter added resistance from the cells themselves. Other laboratories are studying that phenomenon [see "Multidrug Resistance in Cancer," by Norbert Kartner and Victor Ling; SCIENTIFIC AMERICAN, March 1989].

If, as our data indicate, the obstacles to drug dispersion in tumors can be formidable, what might be done to circumvent or eliminate the barriers? No perfect solutions have emerged, but intriguing approaches have been proposed. As ever, early detection and treatment can be beneficial. Compared with established tumors, small ones tend to have a more uniform circulatory system and lower interstitial pressure. They should therefore be easier for conventional and novel drugs to penetrate.

For large tumors, various two- and three-step approaches to treatment are under study. In one of them, an antibody that binds selectively to some molecular constituent of the tumor is linked to an enzyme to form what is called an abzyme. The enzyme chosen is one that has no apparent effect on the body but is capable of converting an inactive form of a selected, small drug molecule (a prodrug) into a tumor-killing agent. A very large dose of the abzyme is injected into the bloodstream, so that it can accumulate in a tumor in spite of slow extravasation and slow interstitial diffusion. High doses can be used because neither the antibody nor the enzyme component significantly harms normal tissue. The prodrug is injected once the abzyme accumulates in the tumor and is cleared from normal tissues and the systemic circulation. Being small, it can readily diffuse out of the tumor circulation; in the interstitial matrix, it should encounter the abzyme, become activated and wend through the tumor, eradicating malignant cells.

Another strategy for evading the barriers to drug dispersion would be to inject patients with liposomes (fatty vesicles) that have been filled with a drug of low molecular weight. The newest generation of liposomes persists for a long while in the blood. Hence, the vesicles should have time to exit from leaky areas of vessels and to reach reasonably high levels in the surrounding interstitium. There the liposomes would grad-



SEGMENT OF A TUMOR includes well-perfused, moderately perfused and nonperfused zones (*left*); a full tumor can have many similarly heterogeneous areas. Drug molecules (*blue*) that reach the interstitium from blood vessels (*red*) immediately attempt to diffuse from well-perfused zones (where the concentration of the drug is the highest) to poorly perfused, low-concentration zones (*black arrows in right image*). But many of the molecules never complete the journey. Some of them are washed away in fluid oozing from the periphery (*gray arrow*). Others may undergo processes—such as binding to the interstitial matrix or degradation—that significantly delay or halt their progress.

ually release the drug, which would proceed to disperse throughout the tumor.

The abzyme and liposome strategies, like others that exploit small molecules, have an Achilles' heel, however. As noted earlier, small molecules can degrade quickly. They can also seep back into tumor vessels and be cleared away from tumors as easily as they diffuse out of blood vessels. They may thus disappear before they have fulfilled their cell-killing responsibilities. Furthermore, high rates of extravasation occur only at sites where vessel walls are leaky.

As research improves understanding of the factors that govern blood flow and the movement of molecules and cells within tumors, workers should be able to invent tools that do not merely evade barriers to drug delivery but actually eliminate them. To be more precise, investigators should be able to increase perfusion in poorly vascularized areas, increase permeability of tumor vessels, reduce interstitial pressure and increase the rate of interstitial transport. Unfortunately, very few laboratories are studying the causes of nonuniform blood flow and high pressure in tumors. Work would proceed more quickly if more investigators became involved.

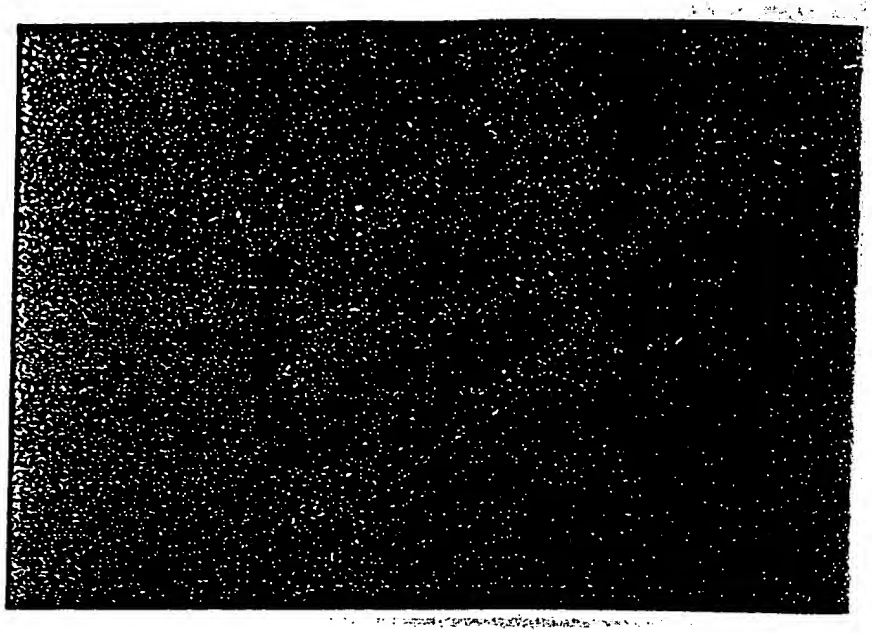
Nevertheless, some progress has been made, particularly in lowering pressure. For example, we recently found that the drugs pentoxifylline and nicotinamide can reduce interstitial pressure in human tumors grown in animals. These agents are also known to increase the oxygen supply in various tumors, which is a benefit for radiation therapy. We also find that irradiating cervical cancers in women sometimes lowers interstitial pressure. Whether such treatment will improve the uptake of drugs in patients remains to be seen. Still, several studies in the scientific literature show that after human tumors grown in animals are irradiated, they accrue increased amounts of injected antibodies.

Another pressure-related strategy may combat tumors confined to one region. The approach calls for mixing a drug with a large amount of fluid and injecting the mixture directly into the center of a tumor. This act would increase the pressure at the core of the tumor relative to the surrounding tumor tissue. As a result, the drug would spread along the induced pressure gradient by convection, from the core through the surrounding region to the periphery. This approach is now being carried out in brain and other tumors.

Alternatively, if a tumor's vascular system could be destroyed completely, no drug would have to extravasate or cope with the interstitium. The persistent, total lack of nourishment would be expected to starve and eventually kill tumor cells. A variety of drugs—among them tumor necrosis factor and monoclonal antibodies that recognize endothelial cells or the subendothelial matrix—have the potential to shut down the blood supply completely. Under some conditions, heating and photodynamic therapies can also impair the vasculature. A number of antiangiogenesis approaches, pioneered by Judah Folkman of Harvard, are under active investigation in many laboratories and clinics.

The white blood cells that are currently being tested against various cancers in human patients may prove useful as antivascular therapies as well. We have recently found that LAK cells adhere to the tumor vasculature and impair the flow of blood in the vessels. This discovery is consistent with the suggestion that in cases where these cells prove helpful to patients, they do so in part by disrupting the tumor's blood supply. Thus, toxicity to tumor cells may not be the only effect of LAK cells in the body. The finding further implies that combining antivascular therapies with therapies that are designed to attack cancer cells could well improve the effectiveness of both types of treatment.

As the age of molecular medicine and gene therapy dawns, scientists need to put expanded effort into uncovering reasons why therapeutic agents that show promising results in the laboratory often turn out to be ineffective in the treatment of common solid tumors. I hope ongoing research into barriers to drug delivery will ultimately ensure that existing and future anticancer drugs live up to their (antiangiogenic) potential.



BRIGHT SPOTS clustered around blood vessels (*dark tubes*) are fluorescently beled liposomes that have seeped from leaky areas of the vessels into the interstial matrix at the periphery of a tumor. Liposomes may one day serve as vehicles for delivering drugs to the interstitium. There the liposomes would presumably release drugs over the prolonged period needed to enhance penetration in the matrix. The extent of liposome transport to the interstitium would be improved, however, if the permeability of nonleaky tumor vessels could somehow be increased.

FURTHER READING

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